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The aim of this prospective, multicenter Phase IIa study was to investigate whether daily intravenous busulfan (IV Bu) with bortezomib is a safe and effective conditioning regimen prior to second, salvage autologous hematopoietic stem cell transplantation (ASCT) for relapsed multiple myeloma (MM) patients.

Thirty patients with relapsed MM were enrolled at 11 centers in the US and Canada. Median age at second ASCT was 59 years (range: 48-73). Median time from first ASCT to second ASCT was 28.0 months (range: 12-119). At the time of second ASCT, 7 (23.3%) patients were in very good partial response (VGPR), 12 (40.0%) in partial response (PR), 2 (6.7%) in stable disease (SD), and 9 (30.0%) in progressive disease (PD).

Patients received a test IV Bu dose (0.8 mg/kg) over 2 hours between Days -12 and -9. The test PK dosing was based on adjusted ideal body weight (AIBW= ideal BW + 0.25 [actual BW − ideal BW]) for all patients except for those whose actual BW is less than or equal to the ideal BW. For those subjects, actual BW was used. Pharmacokinetic (PK) analysis determined Bu exposure as area under the concentration-time curve (AUC), and provided optimized doses so that a total target AUC would achieve 20,000 mMmin. These optimized doses were administered over 3 hours, once daily from Day -5 to Day -2. Confirmatory PK was conducted on Day -5; Bu doses were further adjusted on Days -3 and -2, if needed. Bortezomib (1.3 mg/m$^2$) was intravenously administered on Day -1.

The most common grade 3 or 4 adverse events (CTCAE v3.0) were febrile neutropenia (50.0%), stomatitis (43.3%), and nausea (13.3%). One transplant-related death occurred due to pulmonary complications in a patient with Parkinson's disease on Day 20. There were no reported instances of seizure, worsening neuropathy, or hepatic veno-occlusive disease meeting the Baltimore criteria.

Post-transplant disease response using the 2006 IMWG criteria was available for 28 patients. At 3 months, there were 2 (6.7%) CR, 5 (16.7%) VGPR, 4 (13.3%) PR, 8 (26.7%) SD, and 9 (30.0%) PD. At 6 months, there was 1 (3.3%) stringent CR, 1 (3.3%) CR, 4 (13.3%) VGPR, 7 (23.3%) SD, and 14 (46.7%) PD. Median progression-free survival was 191 days, while median overall survival was not reached.

Test PK showed that 40.0% (n=12/30) of patients had AUC <1,000 (n=11) and AUC >1,500 μM*min (n=1). If body weight-based doses had been used *without test PK*, these patients (40%) would have been dosed outside the target total AUC range (>24,000 or < 16, 000 μM*min) for conditioning. The confirmatory PK on Day -5 revealed that a total AUC fell within the target range in 28 patients (93.3%), while two (6.7%) needed dose reduction on Days -3 and -2.
In conclusion, a combination of IV Bu and bortezomib prior to second ASCT had acceptable safety profile and induced 20% VGPR or better responses at 6 months. No cases of VOD were observed in this group of patients in whom dose optimization using pre-transplant test PK was utilized.

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### Delayed Neutrophil Engraftment Associated with Early CD 8 Polyclonal Lymphocyte Recovery Post Autologous Stem Cell Transplant for Multiple Myeloma

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Delayed engraftment following high-dose chemotherapy and autologous peripheral stem cell transplantation is a rare event. Here, we report two cases of delayed engraftment following autologous peripheral blood stem cell transplant (PBSCT) for Multiple Myeloma (MM) associated with early recovery of polyclonal lymphocytes and response to steroids. Both of our patients were 51 years old at time of transplant and women. The preparative regimen consisted of Melphalan 200mg/m2 prior to stem cell infusion; the stem cell doses were between 2.5 and 2.8 million per kilogram. Per protocol, each received growth factor beginning at day 5 post-transplant. Both patients demonstrated a relative increase in their peripheral blood lymphocyte count without neutrophil recovery by day 15 in one patient and day 25 post-transplant in the other. Peripheral blood for flow cytometry was negative for lymphoproliferative disorder or recurrence of their disease. However, it was noted that their CD4:CD8 ratio was 1:6.5 and 1:6.3 with marked increase in CD8 lymphoctyes. This expansion of CD8+ cells has been implicated in autoimmune cytopenias in patients with autoimmune diseases and was thought to be the cause of cytopenias in our patients. Given the delay in neutrophil recovery, prednisone 1mg/kg was started for concerns that the predominantly CD 8 polyclonal lymphocytes were responsible for suppressing hematopoiesis. Within 48-72 hours of starting steroids, the peripheral blood lymphocytes decreased significantly, and both patients demonstrated neutrophil engraftment followed by platelet engraftment in the subsequent two-week period. Delayed engraftment following autologous PBSCT is uncommon. Viral infection is a common etiology, and rarely, lymphoproliferative processes like large granular lymphocytes (LGL) have been reported post high-dose therapy and autologous PBSCT for MM. In our patients, no viral cause was found and there was no clonal lymphocyte population. In conclusion, this is the first report of post autologous PBSCT delayed engraftment in association with a predominantly CD 8 polyclonal lymphocyte population. This process was readily reversible with corticosteroid therapy and did not necessitate re-transplantation.

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### Evaluating the Effect of High Dose Chemotherapy and Autologous Bone Marrow Transplantation (ASCT) on Hypertension (HTN) in Multiple Myeloma (MM) Patients

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**Background:** A recent study showed that ASCT may reverse kidney failure in one third of multiple myeloma patients, which can lead to improvement in blood pressure. However, there is very limited published data studying the impact of the treatment on blood pressure control.
**Methods:** We conducted a review of electronic medical records of 184 patients with established diagnosis of MM that underwent an ASCT at Karmanos Cancer Institute between January 1st, 2009 and December 31st, 2010. We

recorded data that includes blood pressure (BP) readings 4 weeks before the transplant and then at days 0, 30,100 and 180. Other data includes GFR which is calculated by using the Cockcroft Gault formula at the same intervals, sub-type of MM and Durie-Salmon stage at diagnosis, disease response to therapy, BMI at baseline; and other comorbidities such as diabetes, hyperlipedemia and coronary artery disease. Statistical analyses were performed using the statistical package of SPSS version 18. All *P*-values were 2-sided.

**Results:** In this study 184 patients were included. The sample demographics at baseline are presented in Table 1. Association between BP stages and disease status before ASCT and at day 0 was statistically significant (p=.025 , $X^2$ =14.408); there was no statistically significant association between stages of HTN at 0 , 30, 100 and 180 days after the ASCT in regards to age , race or gender. Mean Systolic and diastolic BP-value showed no statistically significant difference at the same intervals respectively. In addition, there was no correlation between stages of HTN, and stages or type of MM. The only statistically significant association between chronic kidney disease (CKD) stages and BP stages was at day 0 (day ASCT infused) (P=.032, $X^2$ =26.670. The association between CKD stages and disease status at 100 days after melphalan was statistically significant (P=.043, $X^2$ =25.568). The associations between BP stages and BMI stages were borderline or statistically significant at 30 days (P=.054 and $X^2$=16.665), 100 days (P=.026 and $X^2$=18.947) and 180 days(P=.001, $X^2$=27.120).

**Table 1**
Demographic characteristics of the simple

| Patient Characteristics | Number (%) |
|---|---|
| Gender | |
| Male | 100 (54%) |
| Median age years (range) | 59 (33-73) |
| Race | |
| White | 138 (75%) |
| African-American | 41 (22%) |
| Other | 5 (3%) |
| Marital status | |
| Never married | 18 (10%) |
| Now married | 127 (69%) |
| Separated | 13 (7%) |
| Widowed | 6 (3%) |
| Divorced | 20 (11%) |
| Health insurance | |
| Medicare | 180 (98%) |
| Other | 4 (2%) |
| BMI | |
| Normal | 42 (23%) |
| Overweight | 64 (35%) |
| Obese | 42 (23%) |
| Severely obese | 36 (19%) |
| BP stage | |
| Normal | 32 (17%) |
| Prehypertension | 78 (43%) |
| Stage 1 HTN | 64 (35%) |
| Stage 2 HTN | 19 (5%) |
| CKD stage | |
| 1 | 60 (33%) |
| 2 | 82 (45%) |
| 3A | 24 (13%) |
| 3B | 10 (5%) |
| 4 | 5 (3%) |
| 5 | 3 (1%) |
| Myebma stage | |
| IA | 17 (19%) |
| IIA | 25 (14%) |
| IIIA | 130 (71%) |
| IIIB | 12 (6%) |
| Disease status | |
| VGPR | 65 (35%) |
| PR | 57 (31%) |
| CR | 26 (14%) |
| SD | 18 (10%) |
| PD | 16 (9%) |
| SCR | 2 (1%) |
| Melphalan dose | |
| 200 mg | 140 (76%) |
| 140 mg | 44 (24%) |

**Conclusion:** There was no direct effect of ASCT on blood pressure improvement. Other factors such as BMI and disease status at baseline appear to play more roles on Bp control. Majority of our patient were transplanted at early stages of (CKD) which can explain the result. We suggest a prospective study that evaluates the impact of ASCT in MM patients with high BP.

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### Method of Autologous Stem Cell Mobilization Does Not Influence Transplant Outcome

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No standard method for HSC mobilization prior to autologous stem cell transplant (ASCT) exists. We performed a retrospective analysis on consecutive adult patients (pts) undergoing mobilization for ASCT between 1/2009 and 1/2012 to compare efficacy of mobilization method and transplant outcome. Method of mobilization was per the discretion of the attending physician. Chemotherapy and G-CSF (Chemo/G) were used if therapy or cytoreduction was necessary for the underlying malignancy. Per institutional guideline cytokine only mobilization used G-CSF (G) 10 ug/kg daily with apheresis starting on day 5 and plerixafor (G/P) 0.24 mg/kg was added on day 4 if the peripheral blood CD34+ cells/ul was < 15. A total of 343 pts underwent 362 attempts at collection, 192 with G/P, 135 with G alone, and 35 after chemo/G. The median days of apheresis for all three groups was 2 (range 1-4) and the number of cumulative CD 34 cells collected after mobilization was 5.7(0-19), 6.8 (1.9-20.9), and 6.3(0-19) million/kg in the G/P, G, and chemo/G groups, respectively (p=NS). Failure to mobilize CD34 cells was defined as never reaching 10 or greater peripheral blood CD34+ cells/ul or collecting less than 2 million CD34+ cells/kg. Per institutional guideline 192 of 327 collections (59%) starting with G-CSF alone required the addition of plerixafor. Nine of 192 collections (4.6%) in the G/P group failed to mobilize and 2 were rescued with a second G/P mobilization. Twelve of 35 collections (34%) in the chemo/G group failed to mobilize and 8 were subsequently mobilized adequately with G/P. Overall, 11/343 (3.2%) pts failed to mobilize adequate CD34+cells. Engraftment and day 100 transplant outcomes were not different between the groups. In conclusion, the method of mobilizing HSC for ASCT does not seem to affect clinical outcome, pts that fail mobilization after chemo/G for treatment of active disease or cytoreduction can be remobilized with G/P, and our current institutional protocol to begin mobilization with G alone and add plerixafor on day 4 as described above allows a high rate of mobilization success. Further prospective studies are needed to assess pharmacoeconomic and quality of life issues related to HSC mobilization.

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### HDM/ SCT for AL Amyloidosis - A Single Institution 12 Year Experience

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